EXHIBIT D

Technical Report and Analysis
Digitek Tablets

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SommaTech, LLC
June 15, 2010

Executive Summary

Professional Experience

I have more than 35 years of experience working in the pharmaceutical industry, specifically in the areas of production troubleshooting, dosage form development, manufacturing scale-up, technology transfer and project management. My particular technical interest is in the area of solid dosage forms and the physical pharmacy associated with them. I was employed by Novartis for the majority of my career, and have held leadership positions with direct responsibility for senior staff, including international, as well as cross- and multi-functional teams. This has included providing technical development and life cycle management support for a variety of oral solid dosage, novel formulations and therapeutic groups. Additionally, I have served as an invited investigator trainer and liaison for the FDA on various projects and initiatives, affording a unique perspective within Pharmaceutical Regulatory Affairs.

I lead the industry that enabled the implementation of SUPAC IR/MR equipment guidance within FDA/CDER.

As a recognized industry subject matter expert in technology transfer and Quality by Design I have been a welcomed keynote speaker and presenter at many association meetings and conferences. Topics include "Current Industry Practices in Manufacturing Process Validation", "Technology Transfer or Knowledge Transfer for Products and Processes: Which Expedites the Process Most?" and "Life Cycle Management – the Way of the Future?"

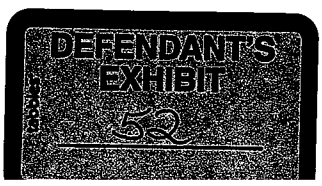
In addition I have written and co-authored numerous articles, technical papers and studies in peer reviewed journal and publications such as *Pharmaceutical Engineering*, *Journal of Pharmaceutical Innovation* and, most recently, *Pharmaceutical Executive*.

Education

- Ph.D. – Pharmaceutical Science, Rutgers University
- M.S. – Pharmaceutical Science, Rutgers University
- B.S. – Pharmacy, Rutgers University

Awards

- Named to "Who's Who in Science & Engineering"
- Letter of commendation for efforts surrounding the SUPAC equipment list, sent by Susan M Setterberg, Mid-Atlantic Region, FDA, dated April 7, 1997.



- "Hammer Award" winner, presented by Vice President Gore's Committee for National Performance Review, 1998
- "Special Recognition Award" presented by CDER Director, Janet Woodcock MD, for invaluable service and technical support to FDA in the development of the SUPAC-IR Equipment Guidance. "I*speak* 18 (1) 1-2 (1998)
- 2007 Recipient of ISPE's prestigious Max Seales Yonker Member of the Year Award

Introduction

This report is the work product from our review of the technical aspects and the manufacturing process for the product Digitek. Digitek is the trade name for digoxin tablets manufactured by Actavis. The product is supplied in two strengths 0.125mg which is a yellow round tablet having a B and 145 on the scored side / plain on the reverse side of the tablet and 0.250mg which is a white round tablet having a B and 146 on the score side / plain on the reverse side of the tablet. The focus of our review centered on the manufacturing processes and technical aspects surrounding that product.

The reason for the review is a response to a request by the Motley-Rice law firm for our expert opinion concerning the events evolving from the manufacture and distribution of digoxin tablets under the trade name Digitek. These events include the final distribution of a batch within which a pharmacist who was dispensing the product in the field reported "double thick "tablets.

Actavis manufactured batch #70924A in November 2007. The technical review included the manufacturing batch record (MPR #14504) as well as related documentation, which included internal investigations, as well as all in-process records through packaging.

Some of our technical observations were subsequently used to confirm the characteristics of the process equipment used for digoxin manufacture by a walk through of the Actavis facility on June 3, 2010. This walk-through was conducted in conjunction with attorney's Peter Miller and Meghan Johnson Cater. During this inspection all the equipment and related questions as related to the equipment were adequately addressed with no open issues.

Blending

Digitek is manufactured using a dry blend / direct compression process. The term dry blend means that the active pharmaceutical ingredient (API) is mixed directly with the required inert / excipient materials without the use of a solvent to form the final blend. The concept of a direct / dry blend is best visualized using the following generalized schematic which outlines typical process steps for pharmaceutical manufacture of oral solid dosage forms such as digoxin tablets.

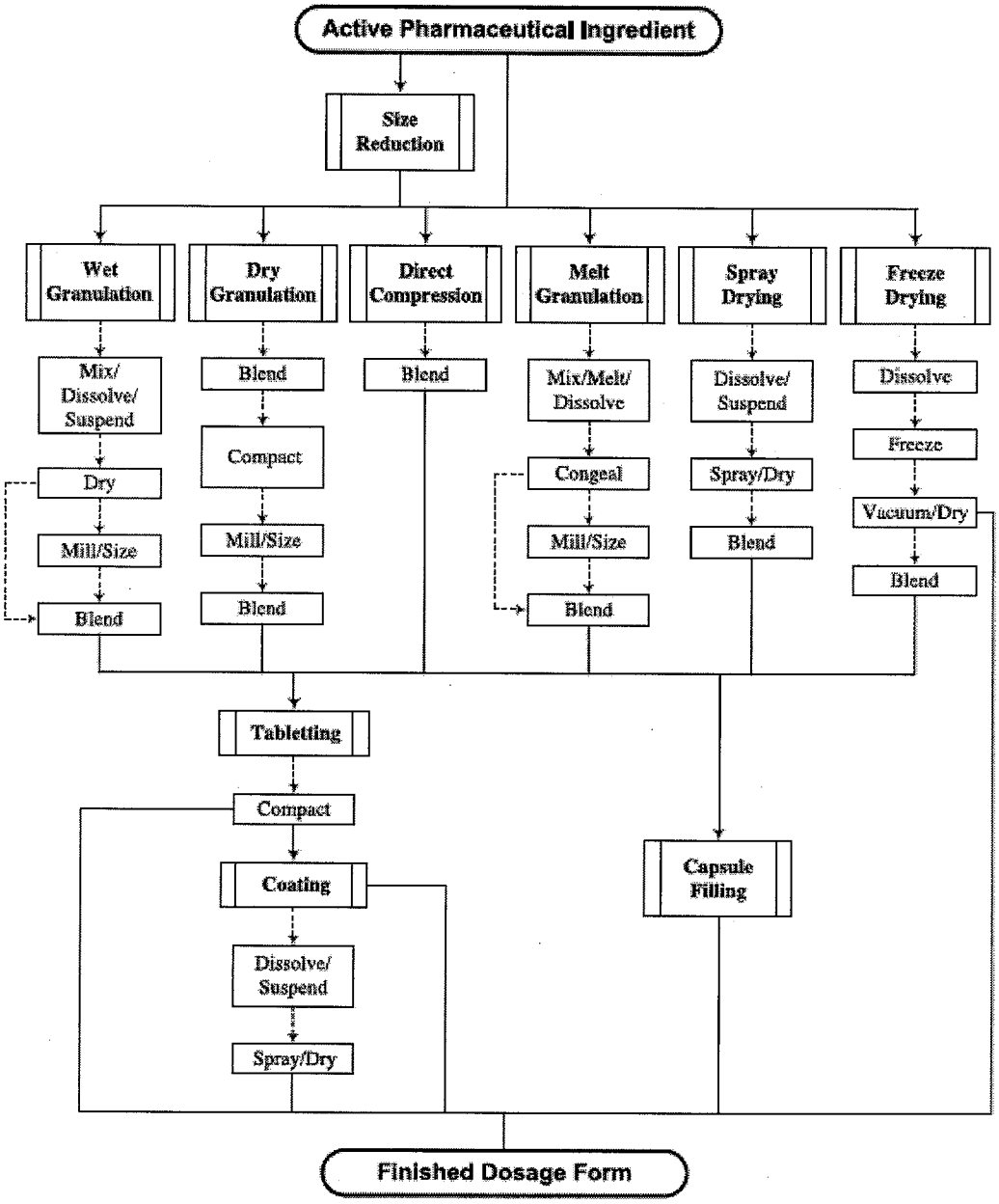


Fig. 4. Common processes for preparing solid oral dosage forms.

(Ref: Zhang et al, Advanced Drug Delivery Reviews, p.371-390, 2003)

The composition of the Digitek blend (504kg.) and the tablet / unit (105.0mg) are shown in the following chart which is taken from MPR#14504 which was used for batch #70924A.

BATCH SIZE: 4,800,000 TABLETS		EXP. DATE:	
THEO. WT.: 105.0 mg	AVG. WT. RANGE (10 TABS): 1.019 - 1.082 g		
ITEM ID NUMBER	RAW MATERIAL NAME	AMOUNT PER UNIT (mg)	QUANTITY REQUIRED (kg)
3115	Corn Starch, NF	7.525	36.12
0111	Digoxin Micronized, USP*	0.125	0.608 (N)
3044	D&C Yellow #10 Aluminum Lake, 15%-20%	0.10	0.480
3000	Croscarmellose Sodium, NF	4.00	19.20
3051	Lactose Hydrous Impalpable, NF*	17.85	85.672 (O)
3088	Starch Pregelatinized, NF	20.0	96.00
3059	Microcrystalline Cellulose, 101, NF	20.0	96.00
3050	Lactose Anhydrous D.T., NF	32.0	153.6
3089	Stearic Acid, NF	3.0	14.40
3081	Silicon Dioxide, NF	0.4	1.920
	TOTAL WEIGHT	105.0	504.0

* Calculate the quantity of Digoxin Micronized, USP (N) and Lactose Hydrous Impalpable, NF (O) based on moisture content of Digoxin Micronized, USP. Refer to Page # 2 and # 3 for calculations.

The amount of digoxin (API) to be used in the batch is corrected to account for the assay value of the API and assures that the desired amount of API is included in the blend. The blending process did not show any procedural issues or unexpected deviations from the established directions and planned deviations as set in place.

The final blend is tested as an in-process control and is required to meet the requirements of 90-110% with an RSD of less than 5.0% for digoxin content using an average of 10 samples taken through-out the blend. The samples are withdrawn from the blender using a sample thief. Three sets of samples are taken to assure material is available should a repeat blend test be required. Batch 70924A was found to meet these requirements without the need to conduct any testing using the replicate samples.

This finished and tested blend is then used to feed the compression equipment / tablet press to make the finished tablets. It should be noted that a change in the specifications was made such that the results are reflective of an “average” of the 10 thief / blend samples rather than on an “individual” of each of the 10 samples. This was properly documented and the regulatory notification as annual reportable had been addressed for the product.

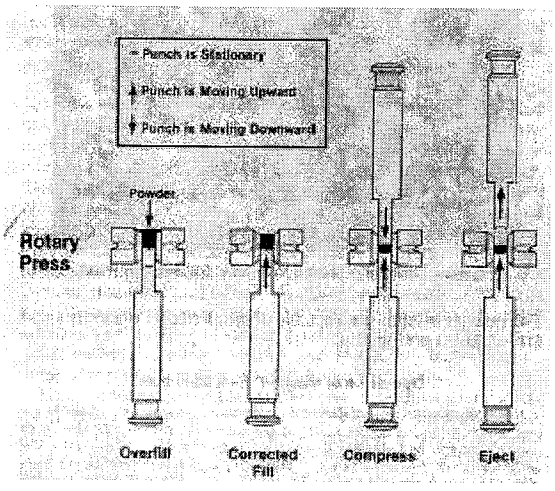
During our review it was clear that blend homogeneity problems had been seen during the testing of other batches. These problems varied in nature but were attributed to analytical testing errors and sample manipulation and recovery from the blending process. It is our experience that blend sampling and testing are difficult. This is appears to hold in this case as the data reviewed would support the firm struggled with this task.

Compression / Tabletting

The tabletting operation was conducted using two tablet machines. These were tablet machines # 67 and #71. Both machines were manufactured by Stokes. The tooling used was flat-faced beveled edge with the debossing previously described for Digitek 0.125mg. The tablet operation is monitored by a tabletting operator who checks machine functionality and confirms the tablets are within the in-process specifications for thickness (2.0 – 3.0 mm) hardness (1.0 – 6.0 kp) and weight (0.097 – 0.114 gm) for ten tablets. These tests are conducted on an hourly basis and recorded through out the compression run for the entire batch (4.8 million tablets).

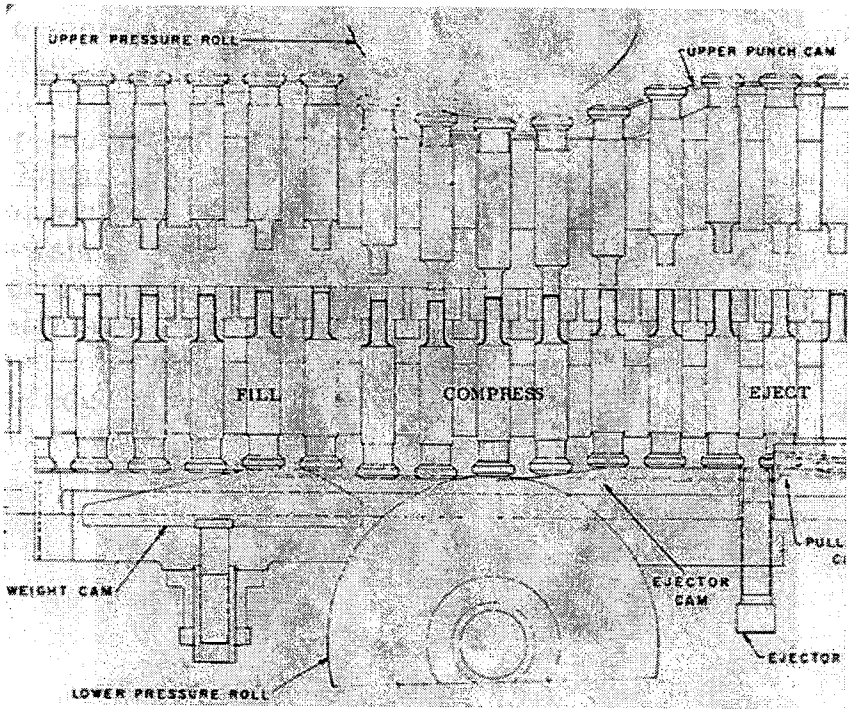
No remarkable events were seen during our review with the exception of an event recorded on page 2711. The records noted that the machine was stopped to clean the tablet tooling (upper and lower punches) since there was some "picking" being observed. The term picking is used to describe the adhesion of some of the tablet blend to the tablet tool tips / punch faces. This was seen on machine #67 and not on # 71. The cleaning was completed and the machine was re-started after confirmation of the tablet specifications were being maintained.

To relate the terms used in tablet formation the following schematic is provided which shows a single station of tablet tooling. This comprises an upper and lower punch as well as a die. It becomes obvious upon inspection of the schematic that the lower punch and the die form a void into which the blend flows. The lower punch moves up after adjustment to achieve the correct fill level. The upper punch then enters the die and applies force to the blend by reducing the available volume between the upper and the lower punch within the confines of the die. Once the punch reaches its maximum distance of penetration it withdraws from the die and the lower punch moves up and ejects the finished tablet out of the die.



(Ref: Remington: The Science and Practice of Pharmacy, 19th Edition, 1995, Mack Publishing, Easton, PA)

The following schematic is provided to better visualize punch movement in the machine as well as to give context to the aspects leading to tablet formation using a tablet machine with multiple stations of tablet tooling like the aforementioned Stokes used for digoxin manufacture.



(Ref: Remington: The Science and Practice of Pharmacy, 19th Edition, 1995, Mack Publishing, Easton, PA)

Multiple upper and lower punches as well as the dies are shown. Additionally the machine location (weight cam), which establishes the amount of material, which flows into the void made by the lower punch and the die, is shown (fill). The weight cam adjusts the setting of the lower punch penetration into the die. This cam may be adjusted up and down thereby changing the penetration of the lower punch and subsequently the available volume for the blend. The result of this adjustment allows a tablet of the desired weight to be compressed. Once the die is filled, the upper and lower punches travel under the pressure rollers, which allows the upper punch to enter the die and reduce the volume available to the blend subsequently forming a tablet. The tablet is ejected (ejection cam) by being pushed out of the die by the lower punch.

This punch movement is accomplished by the machine turret, which rotates the punches and dies over a set of cams and tracks, which guide the punches to the locations shown in the schematic. It should be noted that in the case of the Stokes machines used for Digitek there are two sets of upper and lower punch rollers (front and back) which allow for increased tablet output for the equipment. The mechanics of these rollers are identical. The set up in this case requires that adjustments be made to the

front and back weight controls to assure identical tablet specifications are maintained by both compression stages.

The compressed tablets that come off of the tablet press are then fed through a tablet de-duster as well as a metal detector for dust removal and identification of potential metal fragments. The tablets are collected in labeled bulk storage containers / buckets for transfer to the packaging operation.

We did not consider the sample frequency (every hour) used during the compression phase of the manufacture to be adequate. Based on our experience plus the fact that two machines are in use as well as the amount of material being produced it is difficult to rationalize this sample frequency. One could envision the various problems that can occur in the space of one hour.

Packaging

During the packaging operations the personnel operating the tablet counter saw an over size or "double thick" tablet in the feed tracks of the tablet counter (MTC12). The batch was completed using an extra degree of caution with attention paid to the identification of any additional over-size tablets presenting themselves in the counter tracks. As best as we can determine, there were a total of 5 tablets discovered in this situation as noted on page 2759 for batch 70924A.

Investigation Report

This event resulted in an investigation being opened to determine the root cause of the over size tablets. In addition, the batch was dumped back (removed from the finished packages) for a visual inspection of the entire batch. The investigation report (page 3319-3320) noted that a total of 15 tablets were discovered during the 100% visual inspection.

The investigation report goes on to note that a potential root cause for the occurrence of the thick tablets may be an artifact of the compression machine start-up procedure. This is credible since it is known that to achieve a set series of specifications (weight, thickness and hardness) the mechanics of centering the adjustments will create thick tablets. These over-size tablets are normally captured and discarded.

A potential problem could occur if where these over size tablets may hang up in the tablet de-duster or metal detector. This becomes more likely should the operators fail to remove the de-duster and the metal detector during start up and adjustment. The report goes on to note that as a preventive action the operators were instructed to remove the de-duster and the metal detector during the start-up and the pieces are only to be replaced after the desired specifications have been achieved. This would suggest that these precautions were put in place after the manufacture of batch 70924A.

Commentary on the Investigation

The factors noted during the investigation while relevant to batch 70924A fail to address aspects which must be considered as a continuum with regard to the life cycle of the Digitek product line. This is said in light of the apparent absence of an evaluation of Digitek 0.125mg batches manufactured prior to and after batch 70924A. It has been our experience that it is industry practice to expand technical investigations to address the issues surfaced during the current investigation as a means to probe the technical soundness of decisions made with follow on batches as well using prior batches as a source of guidance for aiding the current investigation.

We were not able to find either the assay or dosage form weights of the offending (over size) tablets as a part of the investigation report. This makes any subsequent evaluation of the data difficult since the nature of the over-size tablets is unknown. This would include the digoxin content of the over-size tablets. This knowledge would allow an estimation of the nature of the additional materials comprising the over-size tablets. The lack of data for the over-size tablets is something that in our opinion is a major flaw in the firm's approach to addressing product problems. It is also taken as indicative of a lack of rigor when addressing product problems in particular when dealing with products having the potency of the API in question.

In the absence of such quantitative information one needs to rely on the observations contained in the records. The recorded observations when considered against a theory that such a tablet would have been randomly produced during the normal manufacture of the tablets is without merit. This is said since the records show only machine stops and re-starts for routine events with the exclusion of the punch cleaning mentioned. This in itself would not support the random compression of an over-size tablet. It would, however, lend credibility to the proposal that the re-start of the machine is a potential source of over-size tablets, which are an artifact of the adjustment procedure (weight, hardness, thickness).

To focus on the potential of tablet carry over by a punch to allow it to be re-compressed with an additional fill amount is unlikely in our experience. This is based on the nature of the Digitek composition as well as the unlikely event that such an event would go unnoticed by the operators.

Compression machines are equipped with an over-load mechanism that is designed to protect the punches. This over-load is mechanical and responds to applied force s, which exceed the established rating set on the equipment. Should the void space (made by the lower punch and the die) be over filled by the blend and a tablet stuck to a punch the system would react to the over-fill by making a distinctive pounding noise. This is something that would not escape the notice of a trained operator. This would also be an event that had taken place at least 20 times (the recorded number of over-size tablets) through out the batch. When this fact is combined with the weight, thickness and hardness settings (mid to upper range) recorded for Digitek the likelihood of this event occurring periodically through out the batch without notice would be small.

The sample frequency of every hour is not addressed and this should be addressed in the report. The need for vigilance during the compression operation cannot be underestimated. Assuring the batch of tablets meets in-process specifications is a primary objective. The presence of a trained operator also assures that the machine is running as expected. The protracted sample frequency being used would suggest a lack of batch oversight in the case of digoxin tablets.

General Overview

What is blending and blend uniformity?
This is the bringing together of the materials (API and inert) needed to realize the manufacture of a solid oral dosage form like Digitek. The objective of blending is to render a homogeneous mass which when randomly sampled those subsequent samples would possess the same composition as the continuous mass from which it is taken. Simply stated this means that the tablet content uniformity will be reflective within an expected degree of variation to that of the powder mass prepared.

There are several types of blending mechanisms. There are also various blending equipment, which are made to accomplish the task of powder mixing. For the most part the use of diffusional blenders is a common approach for powder blending of pharmaceuticals. The diffusional blenders used are v-shaped, bins and double cone. The geometries of these are different but the mechanisms of mixing are similar. These blenders rotate in order to allow the powder within to move and thereby create a degree of flow, shear and particle interaction to achieve a uniform blended powder mass.

The type of blending mechanism we would expect to be reflective of the process used for Digitek would be one of cohesive blending. This means that the powders, which are to be used, are cohesive or lumpy and must be broken up during the blending. This is accomplished by the use of the intensifier bar within each blender used for Digitek. This allows the API to distribute within the powder bed comprised of the other inert ingredients

(Ref: J.T. Carstensen, "Pharmaceutical Principles of Solid Dosage Forms" pages 17 - 29, 1993, Technomic Publishing, Lancaster, PA).

The process of geometric dilution is another technique which may be employed in a blending process. This means that the blend is made in progressively largely volumes to allow for uniform distribution of the material through out the entire blend.

The one aspect that is not fully understood is the scale factors that allow the scale-up of products from laboratory scale to commercial scale. These are aspects that must be addressed using equipment supplier experience, product knowledge acquired during development, and experiments to determine the homogeneity of the desired final blend.

One commonly applied rule that is adhered to in general through out industry is to not change the geometry or shape of the diffusional blender during scale-up. This can result in unexpected problems and it is not uncommon to see development laboratories with an entire series of either bin or v–shaped blender sizes.

We noted during our review that the digoxin process uses two v-shaped blenders during the initial steps of the process. The final step of the process uses a double cone blender. This final step blender is of a different in geometry. It is our experience and is well documented that a change in geometry imparts increased product variability. This blender change combined with the firm's practice of discharging the final blend into drums suggests a process that lacks refinement respect to assuring the homogeneity of the powder blend form batch to batch of digoxin tablets.

(Ref: M. Levin Editor, "Pharmaceutical Process Scale-Up" pages 115 – 132, 2002, Marcel Dekker, New York)

The evaluation of blend uniformity is a difficult task and one that requires a rigidly established plan for removal of samples from the mixing vessel. This plan involves the proper selection of a suitable sampling device. This device is referred to as a thief and it allows a sample probe to be inserted into various locations in the blender. The pattern for the sample selection involves a careful determination of location as well as the top middle and bottom of the blend mass at each of these locations. The size of the samples to be removed are defined by FDA guidance and are usually weight multiples of the final dosage form. For example if the finished tablet will weight is 100mg then the sample should be within a range of 200-210mg. The desired state would be to have a sample that is the exact weight of the final product but the materials, equipment and procedural issues being used may obviate this objective. In the product reviewed the sample size was in the range of 220 – 260mg for a final tablet having a weight of 105mg.

In addition to the sample removal the transfer of the sample to the testing vessels for assay also poses a hurdle that necessitates careful technique to assure the sample weight is maintained during this transfer operation. A faulty technique during sample preparation will result in data that are not reliable and are not reflective of the homogeneity of the blended mass.

The reliability of sample data from the blend is critical to assuring the downstream product meets all quality attributes. In our review it is clear that the firm struggled with this procedure. Repetitive failures at the same blender location are not addressed nor are these anomalies discussed and clarity provided. Lacking this record it is our opinion that the blend sample program was ineffective and not predictive of final product quality.

The following quote is taken from Remington: The Science and Practice of Pharmacy, 19th edition page 1627, 1995

"Recently many companies have reversed their optimism for some direct-compression systems. Some formulations made by direct compression were not as "forgiving" as were the older wet-granulated products. As raw material variations occurred, especially with the drug, many companies found themselves with poorly compactable formulations."

This means that the drug or API used for the product must be well characterized and understood. We did not see any data that indicated the firm did any physicochemical review of the drug in problem batches. This lack of rigorous investigation is critical to assuring "fit for purpose" nature of the drug particularly when it is manufactured in a dry blend process.

What is Compression?
Tablets are the most commonly manufactured type of solid oral dosage form. Tablets are formed by the compression of free flowing granular material. The need for the material to be free flowing is to permit proper filling of the die prior to the application of force. The force applied causes the powder within the die to re-arrange physically and consolidate into the reduced volume that is created by the approach of the upper and lower punch. As the volume continues to be reduced the material undergoes a molecular re-arrangement that is often referred to as "cold welding". This results in the formation of bonds between the molecules of the material and creates a solid monolithic form. This solid form is then ejected from the die by the lower punch.
(Ref: M. Celik, Drug Development and Industrial Pharmacy, p. 767-810, 1992)

The key aspect of tablet manufacture is to establish a process which allows a uniform product with respect to assay / drug content and physical properties (thickness and hardness). The physical properties allow the tablet to be packaged and maintain an elegant form for the patient. The uniformity assures that the patient will get the dose as specified on the product label.

The attributes of the tablet are maintained during manufacture by taking regular samples and checking conformance to established tablet specifications (weight, thickness, hardness) through the entire batch run. Tablet weight assures the proper level of API is contained within each tablet, the thickness and hardness assure proper application of the amount of force to form the tablet. Hardness and thickness are also predictive of how well the tablet will respond to packaging and handling during shipment.

There are compression machines which are equipped with an internal force / pressure* monitoring system. These systems are commonly referred to as weight control systems. They take advantage of the mechanics involving the material filling the die and the subsequent entry of the upper punch to reduce the available volume. In this case should the material contained within the void space of the die and the lower punch exceed the amount which has been manually set by the operator the subsequent increase in force due to the excess material would cause the over-load system to react. This is a result of

the available volume becoming too small for the established space for the lower punch entry.

Compression machines that are equipped with weight control have the ability to measure the applied force by the upper punch by transducers attached to the pressure roller system. Should the set force limit on the monitoring system be exceeded several events take place. First the system automatically rejects the tablets resulting from the compression event that exceeded the set pressure limit. These tablets go to waste and are not part of the finished batch. Second the system automatically adjusts the weight cam. In other words it reduces the amount of material allowed to fill the void space. This automatic adjustment allows the weight of the tablets to be re-centered to the desired weight limits for the product being manufactured. The Stokes compression machines used to make batch 70924A were not equipped with automatic weight control but relied on operator monitoring and specification checks every hour.
(Ref: J. Swarbrick Editor, "Encyclopedia of Pharmaceutical Technology", Second Edition, pages 2669-2688, 2002)

**The terms pressure and force have been used interchangeably in several cases in this report. The term force is the exact terminology to be used when discussing compression of events. While this is a key academic point we have taken some literary license when describing tablet manufacture in this report. The rationale here is to allow the reader to clearly relate the terms presented in the schematic of the rotary tablet machine provided here.*

Formulation and Process
These aspects of the drug, inert ingredients and the process are defined during the development for the product. Part of this development requires that the API in question be compatible with the excipients to be used in the final dosage form. This is determined during a pre-formulation phase. This determines if the combination of inert and API is stable.

The reason the excipients are used is two fold first to achieve the correct dose by dilution of the API and second they allow the blend of API to flow and subsequently be compressed into tablets. Direct compression blends must have materials which allow flow these are lubricants and glidants such as stearic acid and colloidal silicon dioxide. There are materials that are capable of forming a solid during compression such as microcrystalline cellulose. Since the tablet must dissolve / disintegrate in the patients stomach disintegrants are added to help release the API. These materials include pregelatinized starch, croscarmellose and corn starch. Color may also be added for identification or marketing purposes.

Dry blends also require a material that will act to capture the API during blending and help it to distribute through the powder blend. Excipients such as corn starch are effective in achieving this key function. The main point to be taken here is that the inerts must be selected using the API characteristics as well as thereby making the properties of the drug critical to manufacturing a product which meets all quality attributes.

Conclusion and Observations

The drug digoxin is a potent compound with a well-established history of having a narrow therapeutic index. The data for digoxin manufacture that we reviewed show a lack of appreciation of the dangers of this compound. Product problems that were seen were not addressed with the scientific rigor, which in my opinion would be expected in this situation.

The firm lacks the fundamental understanding of the need to define the requirements of the product to be manufactured and take actions within their supply chain as well as within the manufacturing unit to consistently realize a quality product in the case of Digitek.

Some specific points are listed here:

- Blend homogeneity problems are seen during the testing of various batches. These problems varied in nature but were attributed to analytical testing errors and sample manipulation and recovery from the blending process. It is our experience that blend sampling and testing are difficult. This is appears to hold in this case as the data reviewed would support the firm struggled with this task and did not resolve the problems as repetitive failures were noted.
- We do not consider the sample frequency (every hour) used during the compression phase of the manufacture to be adequate. Based on our experience hourly monitoring will not capture machine problems that would result in product defects that could be avoided.
- The over-size tablet investigation report notes that a potential root cause for the occurrence of the thick tablets may be an artifact of the compression machine start-up procedure. This is credible since it is known that to achieve a set series of specifications (weight, thickness and hardness) the mechanics of centering the adjustments will create thick tablets. These over-size tablets are normally captured and discarded. This indicates a lack of adherence to procedures during operations.
- The over-sized tablet report goes on to note that as a preventive action the operators were instructed to remove the de-duster and the metal detector during the start-up and the pieces are only to be replaced after the desired tablet specifications have been achieved. This indicates that these precautions were put in place after the manufacture of batch 70924A.
- The factors noted during the investigation while relevant to batch 70924A fail to address aspects which must be considered as a continuum with regard to the life cycle of the Digitek product line. This is said in light of the apparent absence of an evaluation of Digitek 0.125mg batches manufactured prior to and after batch 70924A. It has been our experience that this failure to investigate further brings into question a systemic problem with the products within the product line.

- We were not able to find either the assay or dosage form weights of the offending (over size) tablets as a part of the investigation report. This makes any subsequent evaluation of the data difficult since the nature of the over-size tablets is unknown. This would include the digoxin content of the over-size tablets. The lack of data for the over-size tablets is something that in our opinion is a major flaw in the firm's approach to addressing product problems. It is also taken as indicative of a lack of rigor when addressing product problems in particular when dealing with products having the potency of the API in question.
- The sample frequency of every hour is not addressed and this should be addressed in the investigation report. The need for vigilance during the compression operation cannot be underestimated. Assuring the batch of tablets meets in-process specifications is a primary objective. The presence of a trained operator also assures that the machine is running as expected. The protracted sample frequency being used suggests a lack of batch oversight in the case of digoxin tablets.
- To focus on the potential of tablet carry over by a punch to allow it to be re-compressed with an additional fill amount is unlikely in our experience. This is based on the nature of the Digitek composition as well as the unlikely event that such an event would go unnoticed by the operators. This of course brings into question again the protracted sample frequency (hourly) used to monitor digoxin compression.
- We noted during our review that the digoxin process uses two v-shaped blenders during the initial steps of the process. The final step of the process uses a double cone blender. This blender is of a different in geometry. It is our experience and is well documented that a change in geometry imparts increased product variability. This blender change combined with the firm's practice of discharging the final blend into drums suggests a process that lacks refinement with respect to assuring the homogeneity of the powder blend from batch to batch of digoxin tablets.
- The reliability of sample data from the blend is critical to assuring the downstream product meets all quality attributes. In our review it is clear that the firm struggled with this procedure. Repetitive failures at the same blender location are not addressed nor are these anomalies discussed and clarity provided. Lacking this record it is our opinion that the blend sample program was ineffective and not predictive of final product quality.
- The Stokes compression machines used to make digoxin are not equipped with automatic weight control but relied on operator monitoring. It is our experience that a weight control system be used for highly potent products. The lack of this automatic system in addition to an hourly in-process testing frequency shows a lack of rigor by the firm during the manufacture of digoxin.

Submitted and prepared by,

Appendix A- Materials Reviewed

In addition to the materials listed in the preceding report, I have also reviewed the following:

Actavis Totowa LLC Timeline- Bates No.: ACTAV 000309763

CGMP statutes

Description of Amide Pharmaceuticals Manufacturing Facility (from ANDA)- Bates No. ACTAV000000417- ACTAV000000424

Methods for Drug Substance and Drug Products (From ANDA)- Bates No. ACTAV000000812- ACTAV000000902

Chart of Compliance Actions regarding Digitek- Bates No. MYLN 000929851- MYLN 000929853

FDA 483 Report to Little Falls -01/10/06-02/08/06- Bates No.: ACTAV 000028908-28914

FDA 483 for Little Falls 7/10/2006 - 8/10/2006 (FOIA Copy)

Establishment Inspection Report (EIR) for Little Falls -7/10/06- 8/10/06 (FOIA Copy)

08/15/2006 Warning Letter from Department of Health and Human Services to Divya Patel

11/17/2006 Letter from Nasrat Hakim at Actavis to FDA in Response to FDA 483 (FOIA Copy)

Final Corrective Action Memo (audit of regulatory status of Actavis) – Bates No.: MYLN 00030303- MYLN 0003030330307

02/01/2007-Revised Warning Letter- Bates No.: ACTAV000028242- ACTAV000028248

9/5/2007 - 9/28/2007- FDA 483 - Little Falls 2007 (FOIA Copy)

EIR 09/05/07-09/28/07 (FOIA Copy)

12/5/2007 Investigation of Deviation Report, Dig Product Lot #70924A1- Bates No.: ACTAV000003317-3336; ACTAV000002598- ACTAV000002622

Batch Record for # 07924A- Bates No.: ACTAV00002650 – ACTAV00002842

04/09/2008 Letter from Jasmine Shah to FDA re: change in QC lab and testing facility from Little Falls to Riverview – Bates No.: ACTAV000006485

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07/21/08 Letter from FDA enclosing EIR for 05/21/08 Inspection- Bates No.: ACTAV0000429520- ACTAV0000429535

08/15/08 Letter to FDA from Actavis Elizabeth from Anthony J. Delicato to Sarah Della Fave at FDA

11/14/2008 Complaint for Permanent Injunction

12/16/2009 Deposition of Richard Dowling

1/18/2010 Deposition of Phyllis Lambridis

1/22/2010 Deposition of Daniel Bitler

1/25/2010 Deposition of Scott Talbot